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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/698,323	10/27/2000	Jeffrey M. Isner	47624DIV(71417)	6299

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EXAMINER	
NGUYEN, QUANG	
ART UNIT	PAPER NUMBER
1633	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/698,323	ISNER ET AL.	
	Examiner	Art Unit	
	QUANG NGUYEN, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *50,52,55-63,65-68,70,72-78 and 84* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *50, 52, 55-63, 65-68, 70, 72-78 and 84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/23/08 has been entered.

Previously presented claims 50, 52, 55-63, 65-68, 70, 72-78 and 84 are pending in the present application, and they are examined on the merits herein.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 50, 55-63, 65-68, 70 and 84 are rejected under 35 U.S.C. 102(e) as being anticipated by Kaplan et al. (US 5,941,868; IDS submitted on 01/09/07) for the same reasons already set forth in the Office Action mailed on 1/23/08 (pages 3-4). ***The same rejection is restated below.***

An embodiment of the instant claims as written encompasses a method for inducing formation of new blood vessels in a mammal having chronic or acute ischemia comprising administering to the mammal an effective fragment of VEGF, wherein the mammal is a rodent or a primate; the following rejection is applied.

Kaplan et al already taught methods for promoting angiogenesis in tissue surrounding a body lumen, particularly including coronary and other arteries in a region of ischemic tissue (e.g., ischemic cardiac tissues surrounding occluded, partially occluded or other coronary arteries), in a human patient comprising transmurally delivering an angiogenic factor to a target site within the blood vessel with exemplary angiogenic factors include VEGF, bFGF, aFGF, EGF, PDGF, fragments thereof as well as combinations thereof (see at least Summary of the Invention; col. 4, lines 16-64; Figure 11). Kaplan et al further taught that the total amount of the angiogenic factor delivered to the target site is typically in the range from 0.1 ug/kg to 100 mg/kg and for a time period ranging from 1 second to 24 hours (col., lines 42-58). Since the disclosed methods of Kaplan et al have the same method steps and starting materials as the method as claimed, it is inherent that the methods of Kaplan et al also produce the same desired effects as claimed.

Accordingly, the teachings of Kaplan et al. meet every limitation of the instant claims as written. Therefore, the reference anticipates the instant claims.

Claims 50, 55-63, 65-68, 70 and 84 are rejected under 35 U.S.C. 102(b) as being anticipated by Ferrara et al. (US 5,332,671) for the same reasons already set forth in

the Office Action mailed on 1/23/08 (pages 4-5). ***The same rejection is restated below.***

An embodiment of the instant claims as written encompasses a method for inducing formation of new blood vessels in a mammal having chronic or acute ischemia comprising administering to the mammal an effective fragment of VEGF, wherein the mammal is a rodent or a primate; the following rejection is applied.

Ferrara et al already taught a method for treating trauma affecting the vascular endothelium (e.g., injuries to the blood vessels or heart as well as the vascular network of organs, wounds, incisions and ulcers) comprising administering to an animal or human suffering from said trauma a pharmaceutical composition comprising an effective amount of a recombinant VEGF (see at least Summary of the Invention; particularly col. 3, line 65 continues to line 19 of col. 4); col. 6, lines 1-12; col. 14, lines 19-34). Ferrara et al also disclosed that used VEGF includes VEGF analogues, variants and fragments having the biological activity of corresponding native VEGF (col. 5, lines 24-68; col. 6, line 13 continues to line 45 of col. 10). Ferrara et al further defined a therapeutically effective amount of VEGF is an amount that is effective to prevent, lessen the worsening of, alleviate the treated condition and in particular the amount is sufficient to enhance the growth of vascular endothelium in vivo (col. 14, lines 35-46), and that the dosage greater than about 0.1 ng/cc to a maximum dose that is efficacy but not unduly toxic (col. 16, lines 47-56). Ferrara et al further taught that VEGF can be combined with other novel or conventional therapies (e.g., growth factors such as aFGF, bFGF, PDGF, IGF, NGF, EGF, TGF-alpha) for enhancing the activity of any of the growth factors

including VEGF, in promoting cell proliferation and repair (col. 16, lines 57-68). Since the disclosed method of Ferrara et al has the same method steps and starting materials as the method as claimed, it is inherent that the method of Kaplan et al also produces the same desired effects as claimed.

Accordingly, the teachings of Ferrara et al. meet every limitation of the instant claims as written. Therefore, the reference anticipates the instant claims.

Response to Arguments

Applicants' arguments with respect to the above rejections in the Amendment filed on 5/23/08 (page 6) have been fully considered but they are respectfully not found persuasive.

Applicant argue basically that independent claim 50 requires the administration of both a VEGF and GM-CSF; and therefore neither Kaplan et al nor Ferrara et al teach the use of both VEGF and GM-CSF in a method for inducing new blood vessels in a mammal having chronic or acute ischemia.

Once again, please note that independent claim 50 recites "**or an effective fragment thereof**". As written, the claim **is not necessarily limited** to a method for inducing formation of new blood vessels in a mammal having chronic or acute ischemia **by administering effective fragments of both VEGF and GM-CSF**. The examiner interprets the claim to encompass the use of an effective fragment of VEGF, an effective fragment of GM-CSF or effective fragments of both VEGF and GM-CSF. As

such, the teachings of either Kaplan et al or Ferrara et al meet every limitation of an embodiment of the instant claims as written.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 50, 52, 55-63, 65-68, 70, 72-73, 75 and 84 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Kaplan et al. (US 5,941,868; IDS submitted on 01/09/07) or Ferrara et al. (US 5,332,671) in view of Bussolino et al. (J. Clin. Invest. 87:986-995, 1991; IDS) for the same reasons already set forth in the Office Action mailed on 1/23/08 (pages 6-9). ***The same rejection is restated below.***

With respect to the embodiment of administering an effective amount of VEGF and GM-CSF of the instant claims, the following rejection is applied.

Kaplan et al already taught methods for promoting angiogenesis in tissue surrounding a body lumen, particularly including coronary and other arteries in a region of ischemic tissue (e.g., ischemic cardiac tissues surrounding occluded, partially occluded or other coronary arteries), in a human patient comprising transmurally delivering an angiogenic factor to a target site within the blood vessel with exemplary angiogenic factors include VEGF, bFGF, aFGF, EGF, PDGF, fragments thereof as well as combinations thereof (see at least Summary of the Invention; col. 4, lines 16-64; Figure 11). Kaplan et al further taught that the total amount of the angiogenic factor delivered to the target site is typically in the range from 0.1 ug/kg to 100 mg/kg and for a time period ranging from 1 second to 24 hours (col., lines 42-58).

Ferrara et al already taught a method for treating trauma affecting the vascular endothelium (e.g., injuries to the blood vessels or heart as well as the vascular network of organs, wounds, incisions and ulcers) comprising administering to an animal or human suffering from said trauma a pharmaceutical composition comprising an effective amount of a recombinant VEGF (see at least Summary of the Invention; particularly col. 3, line 65 continues to line 19 of col. 4); col. 6, lines 1-12; col. 14, lines 19-34). Ferrara et al also disclosed that used VEGF includes VEGF analogues, variants and fragments having the biological activity of corresponding native VEGF (col. 5, lines 24-68; col. 6, line 13 continues to line 45 of col. 10). Ferrara et al further defined a therapeutically effective amount of VEGF is an amount that is effective to prevent, lessen the

worsening of, alleviate the treated condition and in particular the amount is sufficient to enhance the growth of vascular endothelium *in vivo* (col. 14, lines 35-46), and that the dosage greater than about 0.1 ng/cc to a maximum dose that is efficacy but not unduly toxic (col. 16, lines 47-56). Ferrara et al further taught that VEGF can be combined with other novel or conventional therapies (e.g., growth factors such as aFGF, bFGF, PDGF, IGF, NGF, EGF, TGF-alpha) for enhancing the activity of any of the growth factors including VEGF, in promoting cell proliferation and repair (col. 16, lines 57-68).

However, neither Kaplan et al. nor Ferrara et al teach the use of both VEGF and GM-CSF in a method for inducing formation of new blood vessels in a mammal having chronic or acute ischemia or for a method of preventing or reducing the severity of blood vessel damage in a mammal having chronic or acute ischemia.

At the effective filing date of the present application, Bussolino et al already demonstrated that human recombinant G-CSF and GM-CSF are capable of inducing endothelial cells to proliferate and migrate *in vitro*, as well as repair of mechanically wounded endothelial monolayers, together with an exemplification showing that recombinant G-CSF has also angiogenic activity *in vivo*. Additionally, recombinant G-CSF exhibits synergistic effects with bFGF in inducing *in vivo* angiogenesis (see abstract and Methods).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify either the method of Kaplan et al. or the method of Ferrara et al. by also utilizing recombinant G-CSF and/or GM-CSF as angiogenic factors or growth factors to be administered to a patient in need of angiogenesis in tissue surrounding a body lumen,

particularly including coronary and other arteries in a region of ischemic tissue (e.g., ischemic cardiac tissues surrounding occluded, partially occluded or other coronary arteries) or a patient suffering a trauma affecting the vascular endothelium (e.g., injuries to the blood vessels or heart as well as the vascular network of organs, wounds, incisions and ulcers) in light of the teachings of Bussolino et al. Please also note that the treated patient is still subjected to risks associated with ischemic cardiac tissues surrounding occluded or partially occluded as well as trauma affecting the vascular endothelium.

An ordinary skilled artisan would have been motivated to carry out the above modification because Bussolino et al. already demonstrated that both G-CSF and GM-CSF induce endothelial cells to express an activation/differentiation program (including proliferation and migration) related to angiogenesis, and shown at least by exemplification that at least recombinant G-CSF exhibits synergistic effects with at least another endothelial cell mitogen bFGF in inducing *in vivo* angiogenesis. Moreover, Kaplan et al already taught that any angiogenic factor can be utilized with exemplary angiogenic factors include VEGF, bFGF, aFGF, EGF, PDGF, fragments thereof as well as combinations thereof. Similarly, Ferrara et al also taught that VEGF can be combined with other novel or conventional therapies (e.g., growth factors such as aFGF, bFGF, PDGF, IGF, NGF, EGF, TGF-alpha) for enhancing the activity of any of the growth factors including VEGF, in promoting cell proliferation and repair. Furthermore, the advantage of utilizing combinations of angiogenic factors is the attainment of at least the additional effects of administered angiogenic factors together

with potential synergistic effects among various angiogenic factors. The modified method resulting from the combined teachings of either Kaplan et al. or Ferrara et al. and Bussolino et al. is indistinguishable from the presently claimed method.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of either Kaplan et al. or Ferrara et al. and Bussolino et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments with respect to the above rejections in the Amendment filed on 5/23/08 (pages 7-9) have been fully considered but they are respectfully not found persuasive.

With respect to the cited Bussolino reference, Applicants argue basically that Bussolino teaches that the observations were "surprising" and did not find his results predictable, and the data resulted in a "paradox" rather than an understanding and that more experiments need to be done as conclusions can not be drawn from the results in the reference. Accordingly, Bussolino does not provide a reasonable expectation as to how further experiments using his combination of growth factors and cytokines will result, never mind how other combinations will result; and that the Bussolino reference can not provide a motivation to modify another reference.

Firstly, the examiner notes that Applicant mischaracterized the teachings of Bussolino et al. The results of Bussolino et al. **indicated clearly** that human recombinant G-CSF and GM-CSF are capable of inducing endothelial cells to proliferate and migrate *in vitro*, as well as repair of mechanically wounded endothelial monolayers, with an exemplification showing that recombinant G-CSF has also angiogenic activity *in vivo*. Additionally, **recombinant G-CSF exhibits synergistic effects with bFGF in inducing *in vivo* angiogenesis** (see abstract and Methods). Although angiogenic activity of G-CSF is weak relative to bFGF; **the combination of bFGF and G-CSF resulted in an angiogenic response *in vivo* that might be a co-operative interaction or a synergistic effect of these two cytokines**. Regardless of the nature of the interaction, an unexpected angiogenic response was obtained by combining non-angiogenic doses of bFGF and G-CSF *in vivo*. The co-operative effect of G-CSF and bFGF in inducing *in vivo* angiogenesis was **somewhat surprising and intriguing** because Bussolino et al found **no indication of a synergistic action of these two cytokines on HUVEC proliferation and migration *in vitro***; and Bussolino et al concluded that these observed results should be added to a list of factors or conditions **for which *in vitro* modulation of proliferation and migration is not necessarily predictive of in vivo effects on angiogenesis**. The statement "This initial observation needs to be extended" does not refute the observed fact that **recombinant G-CSF exhibits synergistic effects with bFGF in inducing *in vivo* angiogenesis**. The statement could imply that underlying biochemical mechanisms that are responsible for the *in vivo* synergistic effect between G-CSF and bFGF should be investigated.

Secondly, Applicants ignore completely the teachings of the primary references. Particularly, Ferrara et al taught explicitly that VEGF can be combined with other novel or conventional therapies (e.g., growth factors such as aFGF, bFGF, PDGF, IGF, NGF, EGF, TGF-alpha) **for enhancing the activity of any of the growth factors** including VEGF, in promoting cell proliferation and repair (col. 16, lines 57-68). Thus, the concept of using multiple growth factors to attain at least additional as well as synergistic effects (e.g., enhancing effects) for promoting cell proliferation and repair, including angiogenesis, is already established in the prior art as evidenced at least by the teachings of Ferrara et al.

Accordingly, claims 50, 52, 55-63, 65-68, 70, 72-73, 75 and 84 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Kaplan et al. or Ferrara et al. in view of Bussolino et al. for the reasons set forth above.

Claims 50, 52, 55-63, 65-68, 70, 72-78 and 84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kaplan et al. (US 5,941,868; IDS submitted on 01/09/07) in view of Hammond et al. (U.S. Patent 5,880,090) and Asahara et al. (Science 275:964-967, 1997) for the same reasons already set forth in the Office Action mailed on 1/23/08 (pages 9-13). ***The same rejection is restated below.***

With respect to the embodiment of administering an effective amount of VEGF and GM-CSF of the instant claims, the following rejection is applied.

Kaplan et al already taught methods for promoting angiogenesis in tissue surrounding a body lumen, particularly including coronary and other arteries in a region

of ischemic tissue (e.g., ischemic cardiac tissues surrounding occluded, partially occluded or other coronary arteries), in a human patient comprising transmurally delivering an angiogenic factor to a target site within the blood vessel with exemplary angiogenic factors include VEGF, bFGF, aFGF, EGF, PDGF, fragments thereof as well as combinations thereof (see at least Summary of the Invention; col. 4, lines 16-64; Figure 11). Kaplan et al further taught that the total amount of the angiogenic factor delivered to the target site is typically in the range from 0.1 ug/kg to 100 mg/kg and for a time period ranging from 1 second to 24 hours (col., lines 42-58).

However, Kaplan et al. did not teach the use of both VEGF and GM-CSF in a method for inducing formation of new blood vessels in a mammal having chronic or acute ischemia or for a method of preventing or reducing the severity of blood vessel damage in a mammal having chronic or acute ischemia.

At the effective filing date of the present application, Hammond et al. already taught that upon administering an agent including stem cell factor (SCF), granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) into a graft recipient, bone marrow-derived CD34+ endothelial progenitor cells are mobilized into the blood stream (increase in the concentration of the progenitor cells) and to enhance the endothelialization of synthetic vascular grafts (See abstract and example 3 in column 9). Hammond et al. also taught that more than one endothelialization-promoting agent (e.g., fibroblast growth factors, VEGF, angiopoietin-1 described by Suri et al) may be administered concomitantly, and the agent may be administered to the intended graft recipient as much as seven days prior to implantion

of the graft, or may begin on the same day as graft implantation (see col. 3, lines 57-67; col. 4, lines 32-40). An exemplified used dosage for G-CSF is from about 5ug to 15 ug/kg body weight for a total of 3 to 5 days (col. 4, lines 24-31), which is within the preferred dosage range of vascularization modulating agents of the presently claimed invention (1 ug/kg/day to about 100 ug/kg/day).

Hammond et al. also noted that Asahara et al. have shown CD34+ endothelial cell populations are capable of differentiating into endothelial-like cells and the circulating CD34+ or Flk-1+ cells may participate in the repair of ischemic tissue (column 3, lines 28-37). In animal models of ischemia (mouse and rabbit models of induced unilateral hindlimb ischemia), Asahara et al. also taught that syngeneic or autologous endothelial cell progenitors home in and they are incorporated into capillaries and small arteries in the neovascular zones of the induced ischemic limb (See abstract and page 966).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the method of Kaplan et al. by also administering into a mammal having a chronic or acute ischemia an agent such as SCF, GM-CSF and G-CSF to mobilize an effective level of bone marrow-derived endothelial progenitors to home into sites of active angiogenesis to repair ischemic tissues by forming new blood vessels in light of the teachings of Hammond et al. and Asahara et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because Hammond et al. already taught that agents such as stem cell factor (SCF), granulocyte-macrophage colony-stimulating factor (GM-CSF) and

granulocyte colony-stimulating factor (G-CSF) are capable of mobilizing bone marrow-derived CD34+ endothelial progenitor cells into the blood stream of a patient and these endothelial progenitor cells have been demonstrated by Asahara et al. are capable of homing in and incorporated into capillaries and small arteries in the neovascular zones of the induced ischemic limb. Therefore, the further administration of at least GM-CSF would enhance the therapeutic effects for at least a patient in need of angiogenesis in tissue surrounding a body lumen, particularly including coronary and other arteries in a region of ischemic tissue (e.g., ischemic cardiac tissues surrounding occluded, partially occluded or other coronary arteries). Moreover, the modified method would avoid the tedious and time-consuming isolation and purification of progenitor endothelial cells. The modified method resulting from the combined teachings of Kaplan et al. and Hammond et al. and Asahara et al. is indistinguishable from the presently claimed method.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Kaplan et al., Hammond et al., Asahara et al., and coupled with a high level of skill possessed by an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments with respect to the above rejections in the Amendment filed on 5/23/08 (pages 9-11) have been fully considered but they are respectfully not found persuasive.

With respect to the Declaration filed on 2/17/04 under 37 CFR 1.131, Applicants argue that the Declaration provides data from the specific combination of VEGF and GM-CSF as claimed. Specifically, at point 8 and in Exhibit 2, Applicants demonstrate that the combination of VEGF and GM-CSF are effective in promoting angiogenesis in an accepted in vivo model. At the same time that the inventors were performing angiogenic assays using a combination of VEGF and GM-CSF in cornea, they were also performing angiogenesis assays in ischemic animal models using GM-CSF. Applicants further argue that although the Declaration does not include data demonstrating the use of VEGF and GM-CSF in an ischemic limb model, it does not preclude conception of the invention prior to the effective date of Hammond because conception does not require an actual reduction to practice. The inventors understood that the data obtained in the corneal model discussed at point 8 would be predictive of results that would be observed in an ischemic model.

It is noted that nowhere in the Declaration filed on 2/17/04 under 37 CFR 1.131, including at point 8 and in Exhibit 2, is there an evidence indicating or suggesting that Applicants contemplated specifically a method for inducing formation of new blood vessels **in a mammal having chronic or acute ischemia** or a method for preventing or reducing the severity of blood vessel damage **in a mammal having chronic or acute ischemia** by administering to the mammal **an effective amount of VEGF and GM-CSF**

as claimed. At point 8 as well as in Exhibit 2, Applicants simply disclose that **normal mice were pre-treated with GM-CSF**, VEGF-pellets were inserted into corneas of GMCSF-pretreated mice primarily **to attract or to monitor** mobilized endothelial progenitor cells induced by GM-CSF; and not for treating any mammal having chronic or acute ischemia.

Accordingly, prior to September 19, 1997, Applicants did not conceive specifically a method for inducing formation of new blood vessels in a mammal having chronic or acute ischemia or a method for preventing or reducing the severity of blood vessel damage in a mammal having chronic or acute ischemia by administering to the mammal **an effective amount of VEGF and GM-CSF** as now claimed.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir.

1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 50, 55-63, 65-67 and 84 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3-4 and 11 of U.S. Patent No. 5,980,887 for the same reasons already set forth in the Office Action mailed on 1/23/08 (pages 15-16). ***The same rejection is restated below.***

Although the conflicting claims are not identical, they are not patentably distinct from each other because a method for inducing the formation of new blood vessels in an ischemic tissue in a patient (usually a human patient) in need thereof (e.g., treatment for cerebrovascular ischemia, renal ischemia, pulmonary ischemia, limb ischemia, ischemic cardiomyopathy as well as myocardial ischemia) or a method for treating an injured blood vessel in a patient in need thereof, said method **comprises** the same step of administering to the patient an endothelial mitogen that includes a vascular endothelial growth factor, granulocyte/macrophage CSF (encompassing any polypeptide, mutein or portion that is capable of directly or indirectly, inducing endothelial cell growth; see col. 8, lines 29-47 for definition) in the issued U.S. Patent 5,980,887 anticipates the claimed genus of a method for inducing formation of new

blood vessels in a rodent or a primate having chronic or acute ischemia, wherein the method **comprises** administering to the mammal an effective amount of a vascular endothelial growth factor (VEGF) and a GM-CSF, **or an effective fragment thereof**, in the application being examined and, therefore, a patent to the genus would, necessarily, extend the rights of the species or sub-, should the genus issue as a patent after the species of sub-genus.

Claims 50, 52, 55-63, 65-68, 70, 72-78 and 84 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 5,980,887 in view of Hammond et al. (U.S. Patent 5,880,090) and Asahara et al. (Science 275:964-967, 1997) for the same reasons already set forth in the Office Action mailed on 1/23/08 (pages 16-19). ***The same rejection is restated below.***

An embodiment of the instant claims are directed to a method for inducing formation of new blood vessels in a mammal having chronic or acute ischemia or a method for preventing or reducing the severity of blood vessel damage in a mammal having chronic or acute ischemia comprising administering to the mammal an effective amount of a vascular endothelial growth factor (VEGF) and GM-CSF.

Claims 1-11 of U.S. Patent No. 5,980,887 are directed to a method for inducing the formation of new blood vessels in an ischemic tissue in a patient in need thereof or a method for treating an injured blood vessel in a patient in need thereof, said method comprising the step of administering to the patient an endothelial cell mitogen selected

from the group consisting of acidic and basic fibroblast growth factors, vascular endothelial growth factor, epidermal growth factor, transforming growth factor alpha and beta, platelet-derived endothelial growth factor, platelet-derived growth factor, tumor necrosis factor alpha, hepatocyte growth factor, insulin like growth factor, erythropoietin, colony stimulating factor, macrophage-CSF, granulocyte/macrophage CSF and nitric oxide synthase.

The claims of the present application differ from the claims of the U.S. Patent No. 5,880,090 in reciting specifically the step of administering to the mammal an effective amount of a VEGF and GM-CSF.

At about the effective filing date of the present application, Hammond et al. already taught that upon administering an agent including stem cell factor (SCF), granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) into a graft recipient, bone marrow-derived CD34+ endothelial progenitor cells are mobilized into the blood stream (increase in the concentration of the progenitor cells) and to enhance the endothelialization of synthetic vascular grafts (See abstract and example 3 in column 9). Hammond et al. also taught that more than one endothelialization-promoting agent (e.g., fibroblast growth factors, VEGF, angiopoietin-1 described by Suri et al) may be administered concomitantly, and the agent may be administered to the intended graft recipient as much as seven days prior to implantion of the graft, or may begin on the same day as graft implantation (see col. 3, lines 57-67; col. 4, lines 32-40). An exemplified used dosage for G-CSF is from about 5ug to 15 ug/kg body weight for a total of 3 to 5 days (col. 4, lines 24-31), which is

within the preferred dosage range of vascularization modulating agents of the presently claimed invention (1 ug/kg/day to about 100 ug/kg/day).

Hammond et al. also noted that Asahara et al. have shown CD34+ endothelial cell populations are capable of differentiating into endothelial-like cells and the circulating CD34+ or Flk-1+ cells may participate in the repair of ischemic tissue (column 3, lines 28-37). In animal models of ischemia (mouse and rabbit models of induced unilateral hindlimb ischemia), Asahara et al. also taught that syngeneic or autologous endothelial cell progenitors home in and they are incorporated into capillaries and small arteries in the neovascular zones of the induced ischemic limb (See abstract and page 966).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the claims in U.S. Patent No 5,980,887 by also administering into the patient in need of induced new blood vessels in an ischemic tissue or a patient in need of treatment for an injured blood vessel an agent such as SCF, GM-CSF and G-CSF to mobilize an effective level of bone marrow-derived endothelial progenitors to home into sites of active angiogenesis to repair ischemic tissues by forming new blood vessels in light of the teachings of Hammond et al. and Asahara et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because Hammond et al. already taught that agents such as stem cell factor (SCF), granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) are capable of mobilizing bone marrow-derived CD34+ endothelial progenitor cells into the blood stream of a patient and these

endothelial progenitor cells have been demonstrated by Asahara et al. are capable of homing in and incorporated into capillaries and small arteries in the neovascular zones of the induced ischemic limb. Therefore, the further administration of at least GM-CSF would enhance the therapeutic effects for at least a patient in need of induced new blood vessels in an ischemic tissue or a patient in need of treatment for an injured blood vessel. The modified method resulting from the combined teachings of US Patent No. 5,980,887 and Hammond et al. and Asahara et al. is indistinguishable from the presently claimed method.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings 5,980,887, Hammond et al., Asahara et al., and coupled with a high level of skill possessed by an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 50, 55-63, 65-67 and 84 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 49-52, 54-59, 62-65 and 68-69 of the copending Application No. 10/696,391 for the same reasons already set forth in the Office Action mailed on 1/23/08 (pages 19-20). ***The same rejection is restated below.***

Although the conflicting claims are not identical, they are not patentably distinct from each other because a method for inducing new blood vessel growth in myocardial tissue of a mammal in need of such treatment, including a human, said method

comprises the same step of administering to the mammal an effective amount of at least one angiogenic factor or an effective fragment thereof, thereby inducing new blood vessel growth in the myocardial tissue of the mammal, and increasing the frequency of endothelial progenitor cells in the mammal, wherein the angiogenic factor includes VEGF, SCF, GM-CSF, M-CSF or a fragment thereof in the copending Application No. 10/696,391 anticipates the claimed genus of a method for inducing formation of new blood vessels in a rodent or a primate having chronic or acute ischemia, wherein the method **comprises** administering to the mammal an effective amount of a vascular endothelial growth factor (VEGF) and a GM-CSF, **or an effective fragment thereof**, in the application being examined and, therefore, a patent to the genus would, necessarily, extend the rights of the species or sub-, should the genus issue as a patent after the species of sub-genus.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 50, 55-63, 65-67 and 84 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 49, 58-60 and 68-70 of the copending Application No. 10/714,574 for the same reasons already set forth in the Office Action mailed on 1/23/08 (pages 20-21). ***The same rejection is restated below.***

Although the conflicting claims are not identical, they are not patentably distinct from each other because a method for treating ischemic myocardial tissue of a mammal

in need of such treatment, including a human, said method **comprises** the same step of administering to the mammal an effective amount of GM-CSF or an effective fragment thereof, in the copending Application No. 10/714,574 anticipates the claimed genus of a method for inducing formation of new blood vessels in a rodent or a primate having chronic or acute ischemia, wherein the method **comprises** administering to the mammal an effective amount of a vascular endothelial growth factor (VEGF) and a GM-CSF, **or an effective fragment thereof**, in the application being examined and, therefore, a patent to the genus would, necessarily, extend the rights of the species or sub-, should the genus issue as a patent after the species of sub-genus.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

With respect to the above double-patenting rejections, in the amendment filed on 01/09/07 Applicants stated that the rejections will be addressed once allowable subject matter has been identified. In the Amendment filed on 5/23/08, Applicants failed to address the above double-patenting rejections.

Conclusion

No claim is allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the

application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/QUANG NGUYEN, Ph.D./
Primary Examiner, Art Unit 1633